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EXAMINER

O DELL, DAVID K

ART UNIT PAPER NUMBER

1625

MAIL DATE DELIVERY MODE

11/09/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.		Applicant(s)	
	10/514,427		CAI ET AL.	
	Examiner		Art Unit	
	David K. O'Dell		1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 September 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,4-10,20,22,23,25,26,54,57-65,68-74 and 79-101 is/are pending in the application.
- 4a) Of the above claim(s) 65,68-76,79-92,97,98 and 101 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,4-10,20,22,23,25,26,54 and 57-64, 93-96, 99-100 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>22 October 2007</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1, 4-10, 20, 22-23, 25-26, 54, 57-64, 65, 68-74, 79-101 are pending in the current application. Claims 65, 68-74, 79-92, 97, 98, 101 are withdrawn from consideration.
2. This is a National Stage of PCT/US03/15427, filed May 16, 2003, which claims priority to U.S. Provisional Application No. 60/378,079, filed May 16, 2002.

Response to Arguments

3. Applicant's arguments filed on September 17, 2007, have been fully considered and are not fully persuasive. In order to further address applicant's remarks, the traversal of each rejection will be discussed in turn. The rejection of the claims under 35 U.S.C. 112 1st paragraph enablement is maintained for the reasons of record (on the pending claims and the new claims). The submission of commercially available pyridines, is appreciated, and does aid in part in overcoming the how to make rejection, however the chemical limitations that were pointed out by the examiner were stated previously:

"While the inability of the chemist to make compounds that he cannot obtain starting materials is indeed undue experimentation. There is serious reason to doubt the functioning of the scope claimed in applicant's synthesis. For example, piperdine is a base and is the catalyst for applicant's ternary condensation reaction, however piperidine is a good nucleophile and when the extremely electron deficient aldehydes of the instant case are employed it would not be unexpected to see Nucleophilic Aromatic Substitution occur (S_NAr). Indeed numerous examples of this very same reaction are found in the literature see for example Tajimi et. al. US 20060135505 pg.15 reproduced below:"

It is noted on the record that no rebuttal of this evidence or remarks regarding this portion of the rejection were given. The applicant seems to advance the notion that the chemist of ordinary skill can synthesize any compound at will, and that chemical synthesis is in general a trivial undertaking, however this is not the case at all, and as stated in the preface to a recent treatise:

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“Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work.....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious).....” Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

According to the applicant's position, all chemical syntheses are unpatentably obvious.

The rejection with respect to the how to use requirement of 112 1st paragraph was largely ignored or discounted. As per the remarks of September 17, 2007 at pg. 28:

“The Examiner has also based this rejection upon the report by Kemnitzer et al., J. Med. Chem. 47:6299-6310 (2004) which indicates that the identity of the group in

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the 4-position for some related compounds, is critical for activity. Again, Applicants respectfully direct the attention of the Examiner to Example 44 which shows that compounds having a 7-methyl substituent and various A groups have very high caspase activation activity. Moreover, just because a compound may have a lower caspase activation activity does not mean that the compound will be ineffective in inhibiting tumor growth."

The statement that "just because a compound may have a lower caspase activation activity does not mean that the compound will be ineffective in inhibiting tumor growth," may be true, however **a compound must have at least some caspase activity**. It is exceedingly clear that many substituents listed and others embraced by the term "optional substituents" will not function as caspase inhibitors. The examiner had made reference to Kemnitzer et al., *J. Med. Chem.* **2004**, *47*, 6299-6310, to provide evidence of this fact, however it was perhaps not clear to the applicant the nature of the teaching contained in the reference. In order to further clarify as to what the examiner means by the statement: "Inactivity is not lower activity it is a lack of activity", and to make the record extremely clear that the examiner is not taking official notice of this fact, but rather that this conclusion is based on the objective statements of those in the art, the following discussion and publications are submitted that describe exactly what is meant by "activity" or "inactivity".

It is an art recognized phenomenon in pharmacology that compounds having activity above a certain threshold are inactive, meaning that they do not have that activity. In the particular the caspase assay of the instant specification and that used in Kemnitzer et. al. the general threshold is 10 uM or 10,000 nM. See Zhang et. al. "Discovery and SAR of indole-2-carboxylic acid benzylidenehydrazides as a new series of potent apoptosis inducers using a cell

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based HTS assay.” *Bioorganic & Medicinal Chemistry* **2004**, 12, 3649–3655, describing the performance of compounds in the very same assay of the instant specification:

“Table 2 shows that compounds 6c and 9b both inhibited the growth of T47D and DLD-1 cells, while the inactive 6e also does not inhibit growth up to 10 μ M.”

Table 1. Caspase activation activity of substituted indole-2-carboxylic acid benzylidene-hydrazides

Entry	R ₁	R ₂	R ₃	EC ₅₀ (μ M)*		
				T47D	H-1299	DLD
3a	Cl	Me	<i>p</i> -NO ₂	2.2 \pm 0.2	1.4 \pm 0.14	2.0 \pm 0.3
3b	Cl	Me	H	4.0 \pm 0.4	3.5 \pm 0.3	4.3 \pm 0.5
6a	Cl	Me	<i>p</i> -Me	1.04 \pm 0.1	0.7 \pm 0.1	0.7 \pm 0.4
6b	Cl	Me	<i>p</i> -Cl	2.5 \pm 0.07	2.0 \pm 0.4	1.5 \pm 0.07
6c	Cl	Me	<i>p</i> -OMe	2.4 \pm 0.3	0.98 \pm 0.3	2.7 \pm 0.09
6d	Cl	Me	<i>p</i> -NMe ₂	1.3 \pm 0.1	2.8 \pm 0.4	1.6 \pm 0.2
6e	Cl	Me	<i>m</i> -NO ₂	>10	>10	>10
6f	Cl	Me	<i>m</i> -Me	>10	>10	>10
6g	Cl	Me	<i>o</i> -Me	>10	>10	>10
6h	Cl	H	<i>p</i> -NO ₂	5.8 \pm 0.4	4.9 \pm 0.4	>10

Table 2. Comparison of caspase activation activity and inhibition of cell proliferation activity of substituted indole-2-carboxylic acid benzylidene-hydrazides

Compound	EC ₅₀ (μ M)		GI ₅₀ (μ M)	
	T47D	DLD-1	T47D	DLD-1
6c	2.4 \pm 0.3	2.7 \pm 0.09	3.1 \pm 0.7	4.8 \pm 2.3
6e	>10	>10	>10	>10
9b	0.1 \pm 0.06	0.6 \pm 0.1	0.9 \pm 0.2	0.4 \pm 0.05

Data are the mean of three or more experiments and are reported as mean \pm standard error of the mean (SEM).

Here is is very clear that the compound 6e, which is inactive in the caspase activation assay is also inactive in the cell proliferation assay.

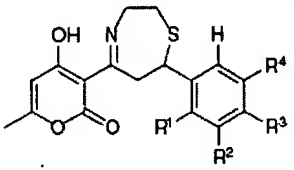
See also the same assay in Drewe et. al. *Bioorganic & Medicinal Chemistry Letters* **2007**, 17, 4987–4990.

“Compound 2b was inactive in T47D cells up to 10 μ M, indicating that a substituent at the 4-position is important for the apoptosis inducing activity. The 4-nitro analog 2c also was inactive up to 10 μ M, suggesting that a strong electron-withdrawing group is not preferred. In comparison, the 4-Cl, 4-F, and 4-SMe analogs 2d–2f were all active, suggesting that a small hydrophobic

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substituent at the 4-position is preferred. The 4-OH analog **2g** was inactive up to 10 μM , suggesting that a hydrophilic group is not preferred at the 4-position. **Compounds 2h–2j were all inactive up to 10 μM** , suggesting that a large group is not preferred. We then explored substituent effects at the meta- and ortho-positions of the phenyl group (Table 1). Among the 3-substituted analogs, compounds 3a–3d were all inactive up to 10 μM . Analog 3e (3-OMe) was the only active compound with an EC_{50} value of 4.5 μM , which was more active than the non-substituted analog 2b. Overall, these data suggested that substitution at the 3-position is not preferred. **Compounds 4a and 4b were both inactive up to 10 μM** , indicating that similar to the 4-position, strong electron-withdrawing group and hydrophilic group are not preferred at the 2-position.”

Table 1. SAR of 5-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-7-phenyl-(E)-2,3,6,7-tetrahydro-1,4-thiazepines in the caspase activation assay



Entry	R ¹	R ²	R ³	R ⁴	EC ₅₀ ^a (μM)	
					T47D	HCT116
2a	H	H	Me	H	1.19 \pm 0.014	1.29 \pm 0.13
2b	H	H	H	H	>10	>10
2c	H	H	NO ₂	H	>10	>10
2d	H	H	Cl	H	2.04 \pm 0.17	2.65 \pm 0.081
2e	H	H	F	H	0.30 \pm 0.036	ND
2f	H	H	SMc	H	2.77 \pm 0.082	2.63 \pm 0.059
2g	H	H	OH	H	>10	ND
2h	H	H	OEi	H	>10	>10
2i	H	H	i-Pr	H	>10	>10
2j	H	H	OBz	H	>10	>10
3a	H	NO ₂	H	H	>10	>10
3b	H	Br	H	H	>10	>10
3c	H	F	H	H	>10	>10
3d	H	OH	H	H	>10	>10
3e	H	OMe	H	H	4.54 \pm 0.17	5.37 \pm 0.10
4a	NO ₂	H	H	H	>10	>10
4b	OH	H	H	H	>10	>10
4c	Br	H	H	H	2.71 \pm 0.13	>10
4d	OMe	H	H	H	2.83 \pm 0.19	4.099 \pm 0.30
5a	OMe	H	Me	H	0.17 \pm 0.017	ND
5b	OMe	H	Cl	H	0.29 \pm 0.063	0.37 \pm 0.050
5c	OMe	H	OMe	H	0.41 \pm 0.069	0.56 \pm 0.010
5d	OMe	H	SMc	H	0.077 \pm 0.007	0.11 \pm 0.013
5e	OMe	H	SO ₂ Me	H	0.13 \pm 0.007	0.25 \pm 0.033
5f	OMe	H	NMe ₂	H	0.33 \pm 0.010	0.53 \pm 0.055
6a	H	OMe	OMe	H	0.57 \pm 0.011	0.79 \pm 0.072
6b	OMe	OMe	H	H	2.66 \pm 0.20	3.69 \pm 0.42
7a	OMe	OMe	OMe	H	0.17 \pm 0.014	ND

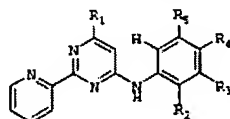
ND, not determined.

^aData are means of three or more experiments and are reported as means \pm standard error of the mean (SEM).See also: Sirisoma et. al. *Bioorganic & Medicinal Chemistry* 2006, 14, 7761–7773:

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"We then came back to explore the SAR of compound 5a. Similar to the SAR of 6a, the 3-methoxy group was found to be important for the activity of 5a. Compound 5b, without the 3-methoxy group, **was not active up to 10 μ M**. The 3-ethoxy analog 5c has good activity and is about 2-fold less active than 5a. This is different from 6e, **the inactive ethoxy analog of 6a**, suggesting that the SAR of the CF₃ series (5a) may not be exactly same as the CH₃ series (6a). The 3-hydroxy analog 5d is about as active as 5a, suggesting that a small and electron- donating group is preferred in the 3-position. Replacement of the 3-methoxy group by other groups (3-methylthiol, trifluoromethoxy, fluoro, trifluoromethyl, and chloro, compounds 5e–5i) all resulted in compounds which were inactive up to 10 μ M. Similarly, the 4-methoxy analog 5j also was inactive."

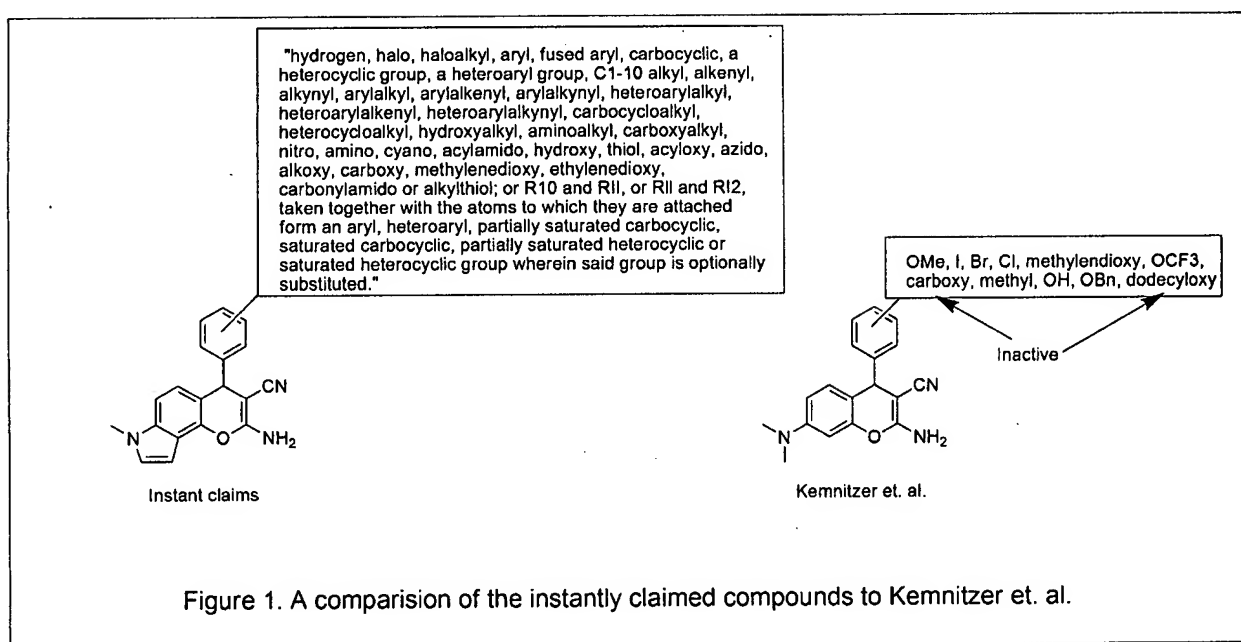
Table 1. SAR of 4-anilino-2-(2-pyridyl)pyrimidines in the caspase activation assay




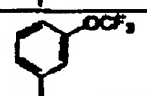
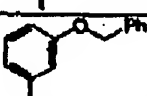
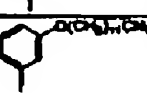
Compound	R ₁	R ₂	R ₃	R ₄	R ₅	EC ₅₀ ^a (μ M)		
						T47D	H1299	HT29
5a	CF ₃	H	OMe	H	H	0.36 \pm 0.17	>10	>10
6a	Me	H	OMe	H	H	0.31 \pm 0.01	>10	>10
6b	Me	H	H	H	H	>10	>10	>10
6c	Me	OMe	H	H	H	>10	>10	>10
6d	Me	H	H	OMe	H	>10	>10	>10
6e	Me	H	OEi	H	H	>10	>10	>10
6f	Me	H	OFz	H	H	>10	>10	>10
6g	Me	H	OCF ₃	H	H	>10	>10	>10
6h	Me	H	F	H	H	>10	>10	>10
6i	Me	H	CN	H	H	>10	>10	>10
6j	Me	H	CF ₃	H	H	>10	>10	>10
6k	Me	H	COMe	H	H	>10	>10	>10
6l	Me	H	COPh	H	H	>10	>10	>10
6m	Me	H	OMe	H	OMe	0.046 \pm 0.003	>10	>10
6n	Me	OMe	H	OMe	H	>10	>10	>10
6o	Me	OMe	H	H	OMe	0.050 \pm 0.005	0.27 \pm 0.01	0.46 \pm 0.06
6p	Me	OMe	OMe	H	H	>10	>10	>10
5b	CF ₃	H	H	H	H	>10	>10	>10
5c	CF ₃	H	OEi	H	H	0.65 \pm 0.07	>10	>10
5d	CF ₃	H	OH	H	H	0.32 \pm 0.02	>10	>10
5e	CF ₃	H	SMe	H	H	>10	>10	>10
5f	CF ₃	H	OCF ₃	H	H	>10	>10	>10
5g	CF ₃	H	F	H	H	>10	>10	>10
5h	CF ₃	H	CF ₃	H	H	>10	>10	>10
5i	CF ₃	H	Cl	H	H	>10	>10	>10
5j	CF ₃	H	H	OMe	H	>10	>10	>10
5k	CF ₃	H	OMe	H	OMe	0.050 \pm 0.006	0.23 \pm 0.04	0.68 \pm 0.02
5l	CF ₃	OMe	H	H	OMe	0.018 \pm 0.001	0.15 \pm 0.02	0.19 \pm 0.04
5m	CF ₃	Me	H	H	OMe	0.055 \pm 0.006	0.37 \pm 0.06	0.54 \pm 0.02
5n	CF ₃	Cl	H	H	OMe	0.18 \pm 0.02	1.66 \pm 0.18	2.78 \pm 0.10
5o	CF ₃	Cl	H	H	Cl	>10	>10	>10
5p	CF ₃	Me	H	OMe	OMe	0.061 \pm 0.009	1.94 \pm 0.59	1.36 \pm 0.01
5q	CF ₃	OMe	H	Cl	OMe	0.12 \pm 0.01	0.38 \pm 0.03	0.52 \pm 0.04

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Now that an objective criteria of inactivity has been established, one must take a look at the work of Kemnitzer et. al. afresh in relation to the instant claims. It may be useful to compare the structure of the compounds side by side, as in figure 1:



Two of Kemnitzer's compounds are completely devoid of activity, in particular compounds 3h and 3k shown below:

Cmpd No.	R	<u>EC₅₀ (μM)</u>		
		T47D	H1299	DLD-1
3h		>10	>10	>10
3i		0.450 ± 0.073	1.14 ± 0.089	0.457 ± 0.030
3j		2.52 ± 0.12	3.56 ± 0.12	4.79 ± 0.07
3k		>10	>10	>10

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In addition Kemnitzer gives us some guidance as to what substituents are tolerated:

"Compounds **1h** and **1i**, with a methoxy group at the 2-position, are >40-fold less active than the 3,4,5-trimethoxy analogue **1b**, suggesting that there might be a space-limited pocket around the 2-position, or due to steric effect, the 2-methoxy group forces the phenyl ring into an unfavorable position. Compound **1j** was >130-fold less active than **1c**, confirming that substitution in the 2-position, is not preferred.....The 3,4-dimethoxy analogue **2d** was >10-fold less potent than **2a**, further supporting the notion that substitution in the 3,5-position is important for activity and substitution in the 4-position contributes little to potency. Similar to what has been observed in the trisubstituted analogues, the 2,3-dimethoxy analogue **2e** was >44-fold less active than **2a**, further confirming that substitution in the 2-position is not preferred."

This makes it clear that the instant claims not meet the how to use requirement of 112 1st paragraph. There are no working examples for the majority of these groups, in fact the only substituents mentioned are: OMe, methylenedioxy, nitro, methyl, chloro, acetate, bromo, fluoro, OH, CN, and methyl, which is not the scope claimed.

The reasoning in the argument that:

"The Examiner also notes that certain benzopyrans are carcinogens. Applicants submit that this assertion has no relevance to the present invention as the claimed compounds are pyrrolo[2,3-h]chromenes and not benzopyrans. Furthermore, it is the responsibility of the U.S. Food and Drug Administration to regulate the safety and effectiveness of drugs, not the U.S. Patent and Trademark Office. The hypothetical carcinogenic activity of the claimed compounds is not an adequate basis to find that the claimed invention is not enabled."

is duplicitous. The applicantt seems to be arguing that since the compounds have a different structure from those of the reference citing the carcinogenic nature of the benzopyrans, we should believe that the carcinogenic activity is absent. Clearly one can see that the compounds of the instant case have a benzopyran ring. This ring of the instant claims has a pyrrole fused to the benzopyran, (see the structures in Figure 1). On the one hand the applicant is

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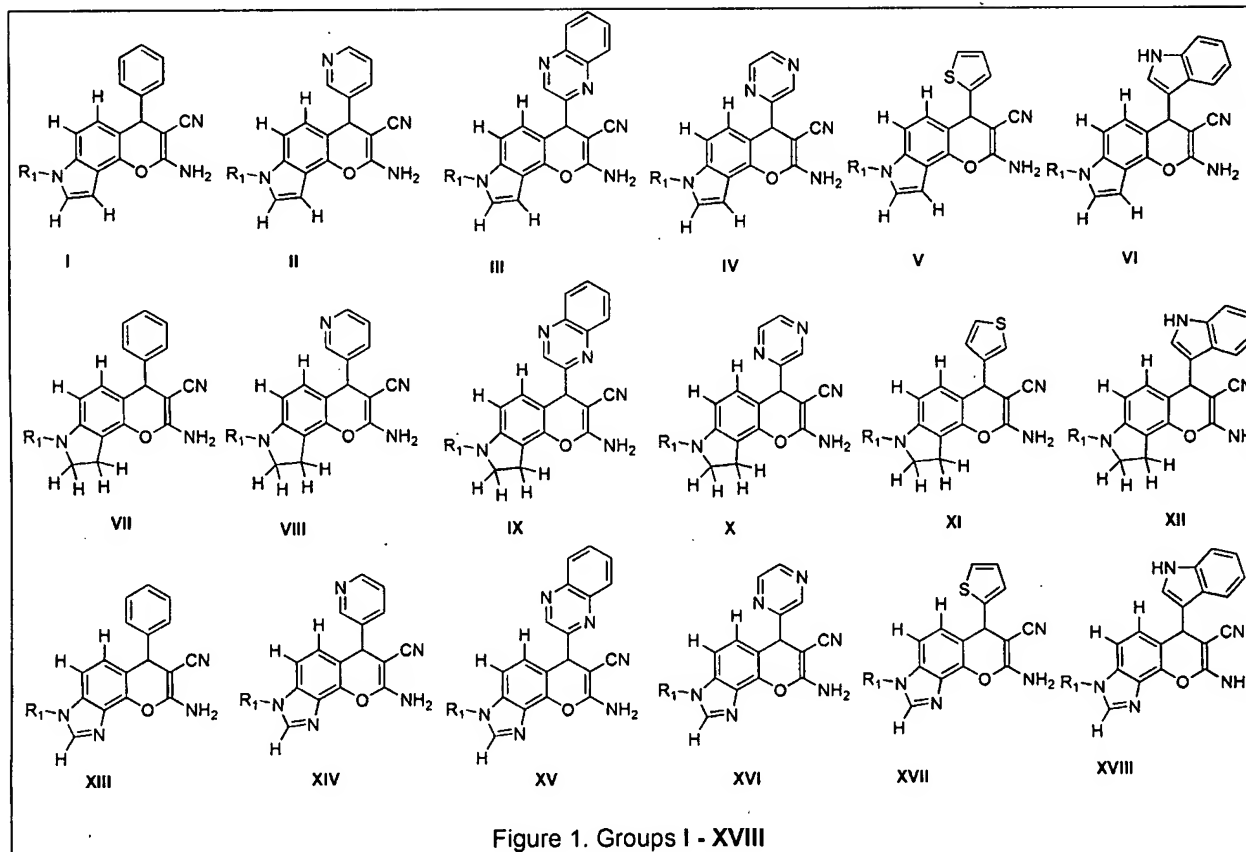
advancing arguments for the enablement of the instant claims and the long list of groups and “optional substituents”, which at its core is stating that the structure of the compounds doesn’t effect activity and that activity is not really important, and on the other hand the applicant is advancing the notion that the instantly claimed compounds are structurally different from the known carcinogenic benzopyrans, thus we wouldn’t expect these materials to have this activity. The examiner requests clarification on this point. The examiner was not rejecting the compounds based on perceived toxicity, but rather highlighting how a structural change may affect the properties of the material.

Based on the applicant’s claim amendments, a new ground of rejection based upon the claim amendments and new claims are made under 103(a), and ODP, see below for the full rejection. This application contains claims drawn to an invention nonelected with traverse in the reply filed on September 17, 2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01. In order to clarify the restriction requirement is given below:

Group I, Claims 1-9, 11-19, 21-23, 54, 57-64 drawn to compounds and compositions possessing a phenyl-pyrrolo[2,3-*h*]chromene core where in applicant’s Markush structure Formula I A is phenyl, D is fused pyrrole, Y=CN, Z=NH₂, or NR₂₂R₂₃ R₃=R₄=R₅=R₂₂=R₂₃=H shown as structure **I** in Figure 1, with the proviso that no compositions contain currently marketed pharmaceuticals. Claims 1-8, 10-20, 24-26, 54, 57-64 drawn to compounds and compositions possessing a 3-pyridyl-pyrrolo[2,3-*h*]chromene core where in applicant’s Markush structure Formula I A is 3-pyridyl, D is fused pyrrole, Y=CN, Z=NH₂, or NR₂₂R₂₃ R₃=R₄=R₅=R₂₂=R₂₃=H shown as structure **II** in Figure 1, with the proviso that no compositions contain currently marketed pharmaceuticals. Claims 1-8, 10-20, 24-26, 54, 57-64 drawn to compounds and compositions possessing a 2-quinoxaliny-pyrrolo[2,3-*h*]chromene core where in applicant’s Markush structure Formula I A is 2-quinoxaliny, D is fused pyrrole, Y=CN, Z=NH₂, or NR₂₂R₂₃ R₃=R₄=R₅=R₂₂=R₂₃=H shown as structure **III** in Figure 1, with the proviso that no compositions contain currently marketed pharmaceuticals. Claims 1-8, 11-20, 54, 57-64 drawn to compounds and compositions possessing a 2-pyraziny-pyrrolo[2,3-*h*]chromene core where in applicant’s Markush structure Formula I A is 2-pyraziny, D is fused pyrrole, Y=CN, Z=NH₂, or NR₂₂R₂₃

[illegible]

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No claims are allowed, this action is FINAL.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness

rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 1, 4-10, 20, 22, 23, 25, 26, 54, 57-64, 92, 93, 95, are rejected under 35 U.S.C. 103(a) as being unpatentable over Drewe, J.A. et. al. WO 2001/034,591 (provided by applicant as FP13 on IDS), OR copending Application No. 11/150,586 (cited by applicant) OR U.S.

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Patent 7,053,117 B2 (cited by applicant as PG Pub 2003/0065018A) OR Drewe, J.A. et. al. U.S. Patent 7,015,328 B2 (cited by applicant at US29). The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

Determination of the scope and content of the prior art

(MPEP 2141.01)

Drewe et. al. teaches compounds that are analogs of the compounds of the instant case that have the same utility. In particular the compounds on pages 74 and following are reproduced below:

Drewe et. al. WO 2001/034,591 teaches number compounds of the instant case as shown below:

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2-Amino-3-cyano-4-(3-methoxy-4,5-methylenedioxyphenyl)-4H-indolo[4,5-b]pyran;

2-Amino-3-cyano-4-(2-bromo-4,5-dimethoxyphenyl)-4H-indolo[4,5-b]pyran;

2-Amino-3-cyano-4-(3-bromo-4,5-dimethoxyphenyl)-4H-indolo[4,5-b]pyran;

2-Amino-3-cyano-4-(3-bromo-4,5-dimethoxyphenyl)-8-methyl-4H-indolo[4,5-b]pyran;

2-Amino-3-cyano-4-(3,4,5-trimethoxyphenyl)-4H-indolo[4,5-b]pyran;

2-Amino-3-cyano-4-(3-nitrophenyl)-4H-indolo[4,5-b]pyran;

2-Amino-3-cyano-4-(3-cyanophenyl)-4H-indolo[4,5-b]pyran;

2-Amino-3-cyano-7-dimethylamino-4-(3,5-difluorophenyl)-4H-chromene;

2-Amino-3-cyano-4-(3,5-dimethoxyphenyl)-4H-indolo[4,5-b]pyran;

Apparently these compounds are named as 4H-indolo[4,5b]pyrans as opposed to pyrrollo[2,3h]chromenes (of the instant case), however this is in fact the same compound core.

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Copending Application No. 11/150,586 teaches:

2-Amino-3-cyano-4-(3-methoxy-4,5-methylenedioxyphenyl)-4*H*-indolo[4,5-*b*]pyran;

2-Amino-3-cyano-4-(2-bromo-4,5-dimethoxyphenyl)-4*H*-indolo[4,5-*b*]pyran;

2-Amino-3-cyano-4-(3-bromo-4,5-dimethoxyphenyl)-4*H*-indolo[4,5-*b*]pyran;

2-Amino-3-cyano-4-(3-bromo-4,5-dimethoxyphenyl)-8-methyl-4*H*-indolo[4,5-*b*]pyran;

2-Amino-3-cyano-4-(3,4,5-trimethoxyphenyl)-4*H*-indolo[4,5-*b*]pyran;

2-Amino-3-cyano-4-(3-nitrophenyl)-4*H*-indolo[4,5-*b*]pyran;

2-Amino-3-cyano-4-(3-cyanophenyl)-4*H*-indolo[4,5-*b*]pyran;

2-Amino-3-cyano-4-(3,5-dimethoxyphenyl)-4*H*-indolo[4,5-*b*]pyran;

U.S. Patent 7,053,117 B2 (cited by applicant as PG Pub 2003/0065018A) teaches:

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EXAMPLE 36**2-Amino-3-cyano-4-(5-bromo-3-pyridyl)-4H-indolo
[4,5-b]pyran**

[0433] To a solution of 5-bromo-pyridine-3-carbaldehyde (94 mg, 0.505 mmol) and malononitrile (34 mg, 0.505 mmol) in anhydrous ethanol (2.5 mL) was added 4-hydroxy-indole (70 mg, 0.526 mmol) and piperidine (0.1 mL, 1.0

and “2-Amino-3-cyano-4-(3,5-dichlorophenyl)-4H-indolo [4,5-b]pyran; 2-Amino-3-cyano-4-(3-chlorophenyl)-4H-indolo [4,5-b]pyran; 2-Amino-3-cyano-4-(3,5-difluorophenyl)-4H-indolo[4,5-b]pyran; 2-Amino-3-cyano-4-(3-fluorophenyl)-4H-indolo[4,5-b]pyran; 2-Amino-3-cyano-4-(3-pyridyl)-4H-indolo [4,5-b]pyran; 2-Amino-3-cyano-4-(5-methyl-3-pyridyl)-4H-indolo [4,5-b]pyran; 2-Amino-3-cyano-4-(5-bromo-3-pyridyl)-4H-indolo[4,5-b]pyran; 2-Amino-3-cyano-4-(5-methoxy-pyridin-3-yl)-4H-indolo[4,5-b]pyran; 2-Amino-3-cyano-4-(3-methoxyphenyl)-4H-indolo[4,5-b]pyran; 2-Amino-4-(3-bromo-4-hydroxy-5-methoxyphenyl)-3-cyano-4H-indolo[4,5-b]pyran; 2-Amino-3-cyano-4-(5-cyano-pyridin-3-yl)-4H-indolo[4,5-b]pyran; 2-Amino-3-cyano-4-(6-methylpyrazin-2-yl)-4H-indolo[4,5-b]pyran; 2-Amino-3-cyano-4-(quinoxalin-2-yl)-4H-indolo[4,5-b]pyran; 2-Amino-3-cyano-4-(3-bromo-4-phosphoric acid-di piperidine salt-5-methoxyphenyl)-4H-indolo[4,5-b]pyran; 2-Amino-3-cyano-4-phenyl-1,4-dihydroquinoline; 2-Amino-3-ethoxycarboxyl-4-(3-bromo-4,5-dimethoxy-phenyl)-4H-indolo[4,5-b]pyran; 2-Amino-3-methylcarboxyl-4-(3-bromo-4,5-dimethoxy-phenyl)-4H-indolo[4,5-b]pyran; 2-Amino-4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-9-methyl-4H-pyrrolo[3,2-h]chromene; 2-Amino-3-cyano-4-(3-pyridyl)-4H-indolo[4,5-b]pyran; “.....etc.

Drewe, J.A. et. al. U.S. Patent 7,015,328 B2 (cited by applicant at US29), teaches the same compounds as Drewe, J.A. et. al. WO 2001/034,591.

Ascertainment of the difference between the prior art and the claims

It is clear that the prior art differs only in the presence of a methyl group.

(MPEP 2141.02)

Drewe et al. do not expressly teach the exact compounds of the instant case.

Finding of prima facie obviousness

Rational and Motivation

(MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use analogs of those of Drewe et. al. to produce the instant invention. Analogs differing only in the substitution of a methyl group for a hydrogen atom, are *prima facie* obvious, and require no secondary teaching. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these compounds on the expectation that such close analogues would have similar properties and upon the routine nature of such experimentation in the art of medicinal chemistry. It would be routine for the chemist to attach a methyl group to the nitrogen of a pyrrole, in order to increase potency and to establish better patent protection for her compounds. See *In re Coes, Jr.* (CCPA 1949) 173 F2d 1012, 81 USPQ 369. This is a very similar situation to that of *Ex parte Bluestone*, 135 USPQ 199 (Bd. Pat. App. & Int. 1961) finding that the N-methyl derivative of a thiazolidinone unpatentably obvious and stated, "A case nearly on all fours with this situation is *Ex parte Weston and Hamlin*, 121 USPQ 428, wherein this Board held that mono substituted N' piperazines were not patentable over di-substituted piperazines of the reference because chemists are well aware of the difference between secondary and tertiary amines and their reactivities including the possibility of further substitution for the hydrogen in the secondary amine. This is the substitution that appellant has made in the Alvord compound."

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12

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USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

One of ordinary skill is also one of “ordinary creativity, not an automaton”. See *Leapfrog Enterprises Inc. v. Fisher-Price. and Mattel Inc.* UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT “An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. , 2007 U.S. LEXIS 4745, 2007 WL 1237837, at 12 (2007) (“The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.”).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1, 4-10, 20, 22, 23, 25, 26, 54, 57-64, 92, 93, 95, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 48-51, 54-81 of copending Application No. 10/514,426. Although the conflicting claims are not identical, they are not patentably distinct from each other because they cover the same compounds and compositions.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. Claims 1, 4-10, 20, 22, 23, 25, 26, 54, 57-64, 92, 93, 95, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17-19, 29, 30, 32, 61, 57 of copending Application No. 11/150,586. Although the conflicting claims are not identical, they are not patentably distinct from each other because they cover the same compounds and compositions.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. Claims 1, 4-10, 20, 22, 23, 25, 26, 54, 57-64, 92, 93, 95, provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 41-63, 73-78 of copending Application No. 11/072,499. Although the conflicting claims are not identical, they are not patentably distinct from each other because they cover the same compounds and compositions.

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This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 4-10, 20, 22, 23, 25, 26, 54, 57-63, 64, 93-96, 99, 100 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compound, does not reasonably provide enablement for the protracted list of substituents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

- (A) *The breadth of the claims;*
- (B) *The nature of the invention;*
- (C) *The state of the prior art;*
- (D) *The level of one of ordinary skill;*
- (E) *The level of predictability in the art;*
- (F) *The amount of direction provided by the inventor;*
- (G) *The existence of working examples; and*
- (H) *The quantity of experimentation needed to make or use the invention*

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

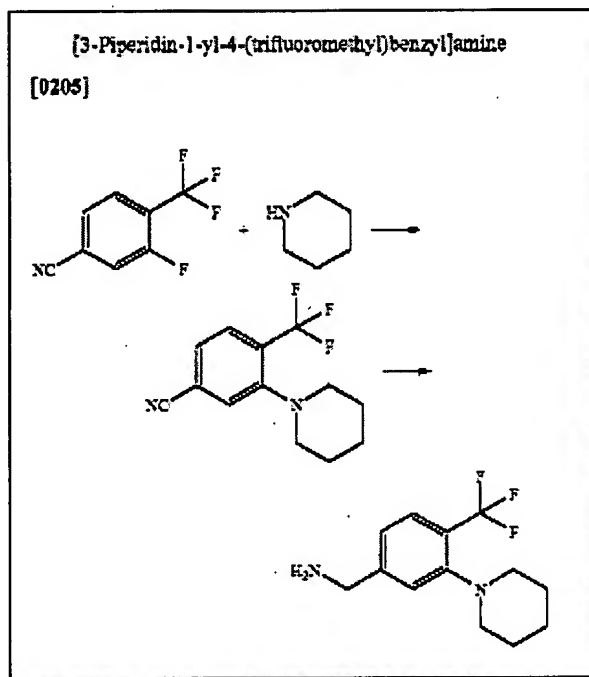
(A) The breadth of the claims: The claims are very broad encompassing a variety of heterocycles, bearing multiple substitutions **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds. **(D) The level of one of ordinary skill:** One of

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ordinary skill is a practicing organic chemist. **(C) The state of the prior art:** Little prior art exists on these complex compounds, however the synthesis will be evaluated on what is known using scientific principles. **(E) The level of predictability in the art:** Chemistry is unpredictable. See *In Re Marzocchi and Horton* 169 USPQ at 367 paragraph 3. **(F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:**

The applicant is relying upon a three component coupling reaction between an aldehyde, malononitrile, and a 4-hydroxy indole. There is serious reason to doubt the functioning of the scope claimed in applicant's synthesis. For example, piperdine is a base and is the catalyst for applicant's ternary condensation reaction, however piperidine is a good nucleophile and when the extremely electron deficient aldehydes of the instant case are employed it would not be unexpected to see Nucleophilic Aromatic Substitution occur (SN_{Ar}). Indeed numerous examples of this very same reaction are found in the literature see for example Tajimi et. al. US 20060135505 pg.15 reproduced below:

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In fact the operability of aldehydes like the one required for the synthesis of 40F is remarkable. One would certainly not expect trifluoromethyl or nitro substituted fluoroaldehydes to react in the desired manner.

While these are clear limitations of the chemistry involved in preparing the compounds, several things become very clear, upon close examination of applicant's data: 1) The substituent R1 can have a marked impact on the activity (asserted utility) of the compounds. For example compounds bearing alkylamino (Example 6) and oxiranyl (Example 19) side chains, show markedly reduced activity compare to (4, 5, 16, 17, 38, 40F). 2) Analogs with 2 substitution were not made or tested, however upon looking to the literature it is clear that these are not compounds that function well in applicants desired manner in compounds that differ only in the presence or absence of a ring-fusion by a methylene or methane carbon (away from the site at

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issue), as stated by (Kemnitzer, W. et. al. Journal of Medicinal Chemistry 2004,47, 6299-6310, cited by applicant NPL27) on pg. 6302 column 1-2

"Compounds **1h** and **1i**, with a methoxy group at the 2-position, are >40-fold less active than the 3,4,5-trimethoxy analogue **1b**, suggesting that there might be a space-limited pocket around the 2-position, or due to steric effect, the 2-methoxy group forces the phenyl ring into an unfavorable position. Compound **1j** was >130-fold less active than **1c**, confirming that substitution in the 2-position, is not preferred.....The 3,4-dimethoxy analogue **2d** was >10-fold less potent than **2a**, further supporting the notion that substitution in the 3,5-position is important for activity and substitution in the 4-position contributes little to potency. Similar to what has been observed in the trisubstituted analogues, the 2,3-dimethoxy analogue **2e** was >44-fold less active than **2a**, further confirming that substitution in the 2-position is not preferred."

3) The identity of the group in the 4- position is critical for activity, Kemnitzer at pg. 6303,

"The nonaromatic cyclohexyl analogue (5a) was >2.5- fold less active than 3l, suggesting that a planar structure of either a phenyl or pyridyl group is preferred in the 4-position of the chromene structure. Extending the nonsubstituted phenyl ring from the 4-position via an ethyl linker (5b) resulted in >3.5-fold reduction in potency relative to 3l, **suggesting that the binding pocket in the 4-position of chromene is size limited.....confirming that there is a size-limited pocket in the 4-position of chromene.**" It is very clear that the long list of groups recited in the claims of the applicant: "R10-R14 are independently hydrogen, halo, haloalkyl, aryl, fused aryl, carbocyclic, a heterocyclic group, a heteroaryl group, C1-10 alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, methylenedioxy, ethylenedioxy, carbonylamido or alkylthiol; or R10 and R11, or R11 and R12, taken together with the atoms to which they are attached form an aryl, heteroaryl, partially saturated carbocyclic, saturated carbocyclic, partially

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saturated heterocyclic or saturated heterocyclic group wherein said group is optionally substituted.” will simply not possess the desired activity due to this size restriction. Moreover, certain benzopyrans are carcinogens (Radwan et. al. Phosphorous, Sulfur, and Silicon 1995, 101, 207-211, sentence 2, cited by applicant).

The specification, while being enabling for making salts and certain esters of the claimed compounds, does not reasonably provide enablement for making prodrugs of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. “The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims”, *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective.

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Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the prodrugs is found not found in the specification. c) There is no working example of a prodrug of a compound the formula I. d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) Banker, G.S. et al, "Modern Pharmaceutics, 3ed.", Marcel Dekker, New York, 1996, pages 451 and 596. in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula

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of claim 1 as well as the presently unknown list of potential prodrug derivatives embraced by claim 1. Thus, undue experimentation will be required to determine if any particular compound is, in fact, a prodrug.

The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has few working examples in this unpredictable art without undue experimentation.

Genetech Inc Vs Nova Nordisk 42 USPQ 2d 1001 "A patent is not a hunting license. It is not a reward for search but compensation for its successful conclusion and patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Conclusion

9. No claims are allowed. This action is FINAL. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Rita Desai can be reached on (571) 272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

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11/6/07